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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,734	03/19/2007	Peter Wisdom Atadja	33366-US-PCT	7764

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
09/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,734	ATADJA ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1,3-5,7-10 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6 and 11-13* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-14 of the instant application are pending. Claims 1, 3-5, 7-10 and 14 are withdrawn from consideration pursuant to Applicant's Arguments/Remarks, filed 07/17/2008, for being drawn to a non-elected group. Thus, instant claims 2, 6 and 11-13 are under consideration for examination on their merits. The instant claims have been examined both with and without considering Applicant's election.

Election/Restrictions

Applicant's election ***without traverse*** of a method for the prevention or treatment of proliferative diseases, in a mammal, which comprises treating the mammal with pharmaceutically effective amounts of a combination of: (a) death receptor ligand, and (b) a histone deacetylase inhibitor of Formula (I) in the reply filed on 07/17/2008 is acknowledged.

Claims 1, 3-5, 7-10 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made ***without traverse*** in the reply filed on 07/17/2008.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

NPL references AM, AR-AT, BM, BR and BS, filed 03/14/2006, have not been considered at this time because Applicant has not provided copies of said references.

Claim Objections

Claim 2 is objected to because of the following informalities.

It appears instant claim 2 depends from withdrawn instant claim 1. Applicant is encouraged to modify instant claim 2 from a dependent to an independent claim format.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 6 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of proliferative diseases, in a mammal, does not reasonably provide enablement for the prevention of proliferative diseases, in a mammal. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP § 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

It is noted that all of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The State of the Prior Art and the Predictability or lack thereof in the art

It is noted that the Applicant provides whereas the combination of the present invention [death receptor ligand and a histone deacetylase inhibitor of Formula (I)] may be used for prevention and treatment of proliferative diseases on page 3, line 1 through page 4, line 4 of the instant specification; however, the generally accepted definition of "prevent" is to keep from occurring, or to anticipate. Therefore, by the Examiner's

broadest reasonable interpretation of the claims to Applicant's method for preventing proliferative diseases, the "prevention" of a proliferative disease lacks enablement due to undue experimentation required to predictably practice the prevention embodiments by Applicant's instant disclosure. Additionally, the art fails to provide compensatory guidance in the prevention of the onset of a proliferative disease. Sonnemann *et al* (*Investigational New Drugs*, Vol. 23, pages 99-109; 2005) also teach the effects of the combination of a death ligand receptor and a histone deacetylase inhibitor, for example, in the Abstract and Discussion; however, this article also references that the treatment of cancers, including leukemia, with said combination improved the apoptotic response post the onset of the proliferative disease. Thus, since neither the instant specification, nor the prior or current art provide sufficient guidance as to how the pharmaceutical combination comprising a death receptor and a histone deacetylase inhibitor could be used to prevent a proliferative disease, it could require undue experimentation to practice the invention as broadly claimed. Additionally, the disclosure is silent with regard to that which makes up and identifies the claimed method for preventing said disease, which is seen to be lacking a clear description via art recognized procedural and methodological steps.

The Amount of Direction or Guidance Present and Presence or Absence of Working Examples

The only direction or guidance present in the instant specification is with regard to the treatment of proliferative diseases. There is no data present in the specification for the "prevention" of said disease. The specification discloses on page 29, Table 1, for

example, wherein the combination administered over a 24 hour period was responsible for approximately 64.9 percent of apoptosis in Patient 5, for example. The guidance in the specification is limited to the disclosure that the composition treats acute myeloid leukemia (AML), for example; however, it is not discussed that said combination can prevent said disease.

The Breadth of the Claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include "prevention" of any proliferative disease.

The Quantity of Experimentation Needed and the Level of Skill in the Art

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prevent *any* proliferative disease. The science of drug development has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The Examiner has extended the examination to disclosed species other than those elected by Applicant; therefore, claims 2, 6 and 11-13 are rejected under 35

U.S.C. 102(e) as being anticipated by Bhalla (U.S. Patent Application Publication No. 2007/0207119 A1).

With regard to instant claims 2, 6 and 11-13, Bhalla disclose, in reference claims 1-4, a method for the treatment of leukemia (a proliferative disease) comprising contacting a target cell with a therapeutic amount of a tumor necrosis factor related apoptosis inducing ligand (Apo-2L/TRAIL) and a histone deacetylase inhibitor (LAQ824; N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide), wherein the leukemia is human acute myeloid leukemia. Bhalla discloses in Fig. 5, for example, in the priority document (U.S. Provisional Application No. 60/319,759, filed 12/06/2002) the effect of the co-treatment of LAQ824 and Apo-2L/TRAIL on cellular apoptosis, thus providing sufficient evidence to serve as prior art under 35 U.S.C. 102(e).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

While taking Applicant's election under consideration, claims 2, 6 and 11-13 are rejected under 35 U.S.C. 103(a) as being obvious over Bhalla (U.S. Patent Application Publication No. 2007/0207119 A1), in view of Remiszewski *et al* (*J. Med. Chem.*, Vol. 46, pages 4609-4624; 2003).

With regard to instant claims 2, 6 and 13, Bhalla disclose, in reference claims 1-4, a method for the treatment of leukemia (a proliferative disease) comprising contacting

a target cell with a therapeutic amount of tumor necrosis factor related apoptosis inducing ligand (TRAIL) and a histone deacetylase inhibitor, wherein the leukemia is human acute myeloid leukemia. Bhalla also discloses wherein said ligand is Apo-2L/TRAIL in the Abstract.

Bhalla fail to disclose wherein the histone deacetylase inhibitor is specifically N-hydroxy-3-[4-[[[2-(***2-methyl***-1*H*-indol-3-yl)-ethyl]-amino]amino]methyl]phenyl]-2*E*-2-propenamide; however, Remiszewski *et al* teach wherein N-hydroxy-3-phenyl-2-propenamides, including N-hydroxy-3-[4[[[2-(***1-methyl***-1*H*–indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide and N-hydroxy-3-[4[[[2-(1*H*-indol-3-yl)ethyl]amino]methyl]phenyl]-(2*E*)-2-propenamide, Compounds 13c and 13g, respectively, are novel human histone deacetylase inhibitors with *in vivo* antitumor activity in the Title and on pages 4618 and 4619. Compound 13c comprises a methyl group in position 1 as opposed to position 2 and Compound 13g is missing said methyl group. MPEP § 2144.09 (II) states, "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

In positional isomerism, a functional group changes position on the chain or ring. As claimed, the positional isomers have substantially similar intended uses as well. As stated *In re Norris* 179 F.2d 970, 84 USPQ 458 (CCPA 1970), a novel useful compound

that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In other words, if the positional isomers of the instant application produced unexpected results that would not be obvious to one of ordinary skill in the art, said isomers would be patentably distinct; however, there is no evidence of such results in the instant application. Thus, the instant claims are *prima facie* obvious over the prior art.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 6 and 11-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 11/147,112 ('112). Although the conflicting claims are not identical, they are not patentably distinct from each other because '112 claims a method for the treatment of leukemia (proliferative disease) comprising contacting a target cell with a therapeutic amount of tumor necrosis factor related apoptosis inducing ligand (TRAIL), such as Apo-2L/TRAIL, and LAQ824 (a histone deacetylase inhibitor; N-hydroxy-3-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide), wherein the leukemia is human acute myeloid leukemia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. C. B. III/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614